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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/583,369	05/24/2007	Peter R. Brink	13533/48203	3149

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EXAMINER

GIBBS, TERRA C

ART UNIT	PAPER NUMBER
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1635

MAIL DATE	DELIVERY MODE
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07/06/2009

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/583,369	BRINK ET AL.	
	Examiner	Art Unit	
	TERRA C. GIBBS	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 February 2009 and 19 March 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-24 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-24 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>2/13/2009</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This Office Action is a response to Applicant's Amendment and Remarks filed March 19, 2009 and February 13, 2009.

Claims 1, 4, 10, and 19-23 have been amended. New claim 24 is acknowledged.

Claims 1-24 are pending in the instant application.

Claims 1-24 have been examined on the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Amendment/Remarks

Applicant's Amendment filed March 19, 2009 is acknowledged. It is noted that the instant application is in compliance with the requirements of 37 CFR 1.121(c).

Information Disclosure Statement

Applicant's information disclosure statement filed February 13, 2009 is acknowledged. The submission is in compliance with the provisions of 37 CFR §1.97. Accordingly, the Examiner has considered the information disclosure statement and a signed copy is enclosed herewith.

Claim Objections

In the previous Office Action mailed September 16, 2008, claim 19 was objected to because the word "connexion" was improperly spelled. **This objection is withdrawn**

in view of Applicant's Amendment filed February 13, 2009. Specifically, the Examiner is withdrawing this objection in view of Applicant's Amendment to claim 19 to correctly spell connexin.

Claim Rejections - 35 USC § 112

In the previous Office Action mailed September 16, 2008, claims 1-14 and 19-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an *in vitro* method of delivering an oligonucleotide or a plasmid expressing an oligonucleotide into a target cell comprising introducing the oligonucleotide into a target cell and contacting the target cell with the donor cell under conditions permitting the donor cell to form a gap junction channel, wherein the gap junction channel is composed of connexin 43, does not reasonably provide enablement for an *in vivo* method of delivering an oligonucleotide or a plasmid expressing an oligonucleotide into a target cell comprising introducing the oligonucleotide into a target cell and contacting the target cell with the donor cell under conditions permitting the donor cell to form a gap junction channel, wherein the gap junction channel is composed of connexin 43. **This rejection is withdrawn** in view of Applicant's Amendment filed February 13, 2009. Specifically, the Examiner is withdrawing this rejection in view of Applicant's Amendment to the claims to specify that claimed method is carried out *in vitro*.

Claim Rejections - 35 USC § 102

In the previous Office Action mailed September 16, 2008, claims 1, 3, 4, 8-12, 14, 20, 21, and 23 were rejected under 35 USC 102(a) as being anticipated by Frendo et al. (Journal of Cell Science, 2003 Vol. 116:3413-3421, submitted and made of record on Applicant's Information Disclosure Statement filed June 19, 2006). **This rejection is withdrawn** in view of Applicant's Amendment filed February 13, 2009. Specifically, the Examiner is withdrawing this rejection in view of Applicant's Amendment to the claims to specify that the method of delivering an oligonucleotide or a plasmid expressing an oligonucleotide into a target cell requires that the oligonucleotide or a plasmid expressing an oligonucleotide is delivered by traversing the gap junction. It is noted that Frendo et al. do not teach that the oligonucleotide or a plasmid expressing an oligonucleotide is delivered by traversing a gap junction.

In the previous Office Action mailed September 16, 2008, claims 1, 3, 4, 6, 10-12, 14, 20, 21, and 23 were rejected under 35 USC 102(b) as being anticipated by Li et al. (Journal of Cell Biology, 1996 Vol. 134:1019-1030). **This rejection is withdrawn** in view of Applicant's Amendment filed February 13, 2009. Specifically, the Examiner is withdrawing this rejection in view of Applicant's Amendment to the claims to specify that the method of delivering an oligonucleotide or a plasmid expressing an oligonucleotide into a target cell requires that the oligonucleotide or a plasmid expressing an oligonucleotide is delivered by traversing the gap junction. It is noted that Li et al. do

not teach that the oligonucleotide or a plasmid expressing an oligonucleotide is delivered by traversing a gap junction.

In the previous Office Action mailed September 16, 2008, claims 1, 3, 4, 10-12, 14, 19, 20, 21, and 23 were rejected under 35 USC 102(b) as being anticipated by Burt et al. (American Journal of Physiology: Cell Physiology, 2001 Vol. 280:C500-C508). **This rejection is withdrawn** in view of Applicant's Amendment filed February 13, 2009. Specifically, the Examiner is withdrawing this rejection in view of Applicant's Amendment to the claims to specify that the method of delivering an oligonucleotide or a plasmid expressing an oligonucleotide into a target cell requires that the oligonucleotide or a plasmid expressing an oligonucleotide is delivered by traversing the gap junction. It is noted that Burt et al. do not teach that the oligonucleotide or a plasmid expressing an oligonucleotide is delivered by traversing a gap junction.

Claim Rejections - 35 USC § 103

In the previous Office Action mailed September 16, 2008, claims 1-14 and 19-23 were rejected under 35 U.S.C. 103(a) as being unpatentable over either Frendo et al. (Journal of Cell Science, 2003 Vol. 116:3413-3421, submitted and made of record on Applicant's Information Disclosure Statement filed June 19, 2006), Li et al. (Journal of Cell Biology, 1996 Vol. 134:1019-1030), or Burt et al. (American Journal of Physiology: Cell Physiology, 2001 Vol. 280:C500-C508) in view of Hammond et al. (Nature

Reviews, 2001 Vol. 2:110-119). **This rejection is withdrawn** in view of Applicant's Amendment filed February 13, 2009. Specifically, the Examiner is withdrawing this rejection in view of Applicant's Amendment to the claims to specify that the method of delivering an oligonucleotide or a plasmid expressing an oligonucleotide into a target cell requires that the oligonucleotide or a plasmid expressing an oligonucleotide is delivered by traversing the gap junction. It is noted that neither Frendo et al., Li et al., Burt et al., nor Hammond et al. teach that the oligonucleotide or a plasmid expressing an oligonucleotide is delivered by traversing a gap junction.

Applicant's Amendment filed February 13, 2009 necessitated the new ground(s) of rejection presented below:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of delivering an oligonucleotide into a target cell *in vitro*, the method comprising a) introducing the oligonucleotide into a donor cell and b) contacting the target cell with the donor cell under conditions permitting the donor cell to form a gap junction channel with the target cell, whereby the oligonucleotide is delivered into the target cell from the donor cell by traversing the gap

junction, wherein the oligonucleotide is between 12-24 nucleotides in length and the gap junction channel is composed of connexin 43, does not reasonably provide enablement for a method of delivering an oligonucleotide or a plasmid expressing an oligonucleotide into a target cell comprising a) introducing the oligonucleotide or the plasmid into a donor cell *in vitro*, and b) contacting the target cell with the donor cell under conditions permitting the donor cell to form a gap junction channel with the target cell, whereby the oligonucleotide, the plasmid expressing the oligonucleotide or a peptide product thereof is delivered into the target cell from the donor cell by traversing the gap junction. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This is a scope enablement rejection.

There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

“Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.”

The nature of the invention and the breadth of the claims:

The claimed invention is drawn to a method of delivering an oligonucleotide or a

plasmid expressing an oligonucleotide into a target cell comprising a) introducing the oligonucleotide or the plasmid into a donor cell *in vitro*, and b) contacting the target cell with the donor cell under conditions permitting the donor cell to form a gap junction channel with the target cell, whereby the oligonucleotide, the plasmid expressing the oligonucleotide or a peptide product thereof is delivered into the target cell from the donor cell by traversing the gap junction.

It is noted that Applicant's Specification at page 7, lines 11 and 12 discloses:

"The experiments determined that oligocomplexes such as DNA or RNA sequences of defined length are able to pass through a gap junction channel"

The specification at page 7, lines 23-25 also discloses:

"The results demonstrated that all three single stranded forms pass through gap junction channels composed of Cx43"

The amount of direction or guidance and presence/absence of working examples:

Applicants have demonstrated that only oligonucleotides of 12-24 nucleotides in lengths are able to traverse gap junction channels composed on connexin 43 (Cx43). See Figures 1a-1d, Figure 2A, and the specification at page 7, lines 23-25, for example. The Examiner has found in the prior art that only oligonucleotides of 12-24 nucleotides in lengths are able to traverse gap junctions composed of Cx43. See Valiunas et al. (J. Physiol 568.2:459-468, 2005). Specifically, Valiunas et al. disclose:

"The rate of transfer declined with increasing length of the oligonucleotide" (see Abstract).

"This suggested that Cx43 but not Cx32/Cx26 channels allowed the cell-to-cell movement of the siRNA" (see Abstract).

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"These data suggest that synthetic nucleotides selectively pass through Cx43 but not Cx26 or Cx32 gap junction channels" (see sentence bridging pages 462 and 463).

"Fluorescently labeled oligonucleotides, simulating siRNAs, were generated (12-mer, 16-mer, and 24-mer). They too were found to permeate gap junction channels composed of Cx43, but not Cx26/Cx32" (see page 466, first column).

"These data support the novel hypothesis that gap junction channels have connexin-specific permeability to siRNA" (see page 466, first column).

"At this stage, we have identified only Cx43 channels as being permeable to siRNA" (see page 466, second column).

The specification as filed does not provide sufficient guidance or appropriate examples that would enable a skilled artisan to use the claimed methods for delivering, by traversing a gap junction channel, any/all sizes of oligonucleotides other than oligonucleotides that are 12-24 nucleotides in length. Additionally, a person skilled in the art would recognize that based on the teachings of Valiunas et al., coupled with specific statements found in Applicant's specification, gap junction channels have connexin-specific permeability to oligonucleotides, including siRNA oligonucleotides. Thus, although the specification contemplates the use of any oligonucleotide, including plasmid DNA expressing oligonucleotides, such a disclosure would not be considered enabling since Valiunas et al. teach that the length of the oligonucleotide plays an important factor in gap junction traversal. Furthermore, although the specification contemplates gap junctions composed of any connexin protein, such a disclosure would not be considered enabling since the state of the art of using connexin 26 or connexin 32, for example, to deliver oligonucleotides by gap junction channel traversal is highly unpredictable. See Valiunas et al.

The state of the prior art and the predictability or unpredictability of the art:

The claimed invention is a class of invention which the CAFC has characterized as “the unpredictable arts such as chemistry and biology.” *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The level of skill in the art:

The relative skill of those in the art is considered to be high, being a graduate student or post-doctoral fellow in a biological science.

The quantity of experimentation necessary:

A review of the instant application finds adequate guidance for an *in vitro* method of delivering oligonucleotides of 12-24 nucleotides in length via gap junction channels composed of connexin 43. Although Applicants clearly recognize the potential of using other oligonucleotides, Applicants only teach that oligonucleotides of defined lengths are able to pass through a gap junction channel. See Figure 2A for example. No technical guidance or exemplary disclosure is provided regarding methods of delivering other oligonucleotides, as the claims broadly encompass oligonucleotides expressed from plasmid DNA. As the reference of Valiunas et al. above indicates, the rate of gap junction channel traversal is dependent on the length of the oligonucleotide.

Thus, it is maintained that the prior art at the time of Applicant's filing would not enable the disclosure of a method of delivering any oligonucleotide into a target cell by traversing a gap junction composed of any connexin protein. This is particularly true since the prior art taught that gap junction channels have connexin-specific permeability to specific oligonucleotides of specific lengths. See Valiunas et al. Accordingly, one

skilled in the art, being unable to use the prior art for such guidance, must necessarily find such guidance from the specification. However, one of skill would not find the guidance provided in the specification enough to overcome the unpredictability and challenges of methods of delivering any oligonucleotide into a target cell by traversing a gap junction composed of any connexin protein, particularly in view of Valiunas et al.

In order to practice the invention using the specification and the state of the prior art as outlined above, the quantity of experimentation required to practice the invention as claimed would require the *de novo* determination and analysis of those oligonucleotides that can successfully traverse a gap junction channel such that the oligonucleotide is delivered to a target cell *in vitro*. As supported by Valiunas et al., such analysis is replete with trial and error experimentation. Such experimentation represents an inventive and unpredictable undertaking in itself, with each of the many intervening steps, not providing any guarantee of success. Given the art recognized unpredictability of delivering an oligonucleotide into a target cell by traversing a gap junction channel composed of a connexin protein, this determination would not be routine and would require undue trial and error experimentation.

Due to the scope of the claims, one of skill in the art would be required to further undertake extensive trial and error experimentation to determine those oligonucleotides that can successfully traverse a gap junction channel such that the oligonucleotide is delivered to a target cell. Since the specification fails to provide any real guidance for the oligonucleotides that can successfully traverse a gap junction channel such that the oligonucleotide is delivered to a target cell, other than oligonucleotides that are of a

specific size, and since resolution of the various complications in regards to which connexin proteins allow gap junction channel traversal of oligonucleotides is unpredictable, one of skill in the art would have been unable to practice the invention over the scope claimed, without engaging in undue trial and error experimentation.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached from 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, James "Doug" Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

June 28, 2009
/Terra Cotta Gibbs/

/Sean R McGarry/

Primary Examiner, Art Unit 1635